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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

KISHORE, GOLLAMUDI S

ART UNIT	PAPER NUMBER
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1615

DATE MAILED: 03/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/555,986	CEVC, GREGOR	
	Examiner	Art Unit	
	Gollamudi S Kishore, PhD	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 November 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 58-98 and 100-198 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 58-98 100-198 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

The amendment dated 11-24-03, the request for the extension of time and change of address dated 2-6-04 are acknowledged.

Claims included in the prosecution are 58-98 and 100-198.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
2. Claims 58-98 and 100-198 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for specific combination of substances (first substance, second substance and third substance), specific liquid medium, does not reasonably provide enablement for claims as claimed with confusing terminology. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Claims are recited in a very vague and confusing way and the

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specification does not provide adequate guidance as to the nature of the claimed composition.

Applicant's lengthy arguments have been fully considered, but are not found to be persuasive. Most of the arguments have been extensively addressed before. The essence of applicant's arguments appear to be that either the terms are described in the specification or well known to one of ordinary skill in the art. These arguments are not found to be persuasive. The issue here whether one of ordinary skill in the art would be able to select the components and practice the invention without undue experimentation based on instant disclosure. It is the examiner's position that one will not be able to. The specification does not in clear terms define and describe what compounds fall in each category and in examples, applicant uses a combination of phosphatidylcholine, sodium cholate and insulin (some examples contain phosphatidylglycerol in addition). According to claim 58, the solubility of the second amphipathic substance (presumably it is selected from the group consisting of surface-active substances and surfactants) is greater than the solubility of the first substance". Taking applicant's examples, phosphatidylcholine appears to be the first substance and sodium cholate, the second substance; phosphatidylcholine is not soluble at all in aqueous medium and sodium cholate is highly soluble. Sodium cholate being a hydrophilic surfactant, one would expect insulin (which is also hydrophilic) to dissolve in sodium cholate and segregate in the aqueous interior and not associate with the extended surface of the second substance. There are no examples showing the association of insulin on the extended

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surfaces of either the first substance or the second substance (if one of ordinary skill in the art is able to determine which is the first substance and which is second substance which forms extended surfaces). In essence, the specification is very confusing and not enabling for one of ordinary skill in the art to practice the invention without undue experimentation. The rejection is maintained.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 58-98 and 100-198 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The amended claims have the same issues, which existed before. As already indicated, if a substance is soluble in a liquid (regardless of the degree of solubility) how can it form an extended surface? What is meant by an extended surface? According to claim 58 (in other independent claims also), the molecules of the third substance associate with the extended surfaces formed by the first substance and the second substance. As pointed out above, according to the examples, sodium cholate is the second substance and insulin is the third substance. How can insulin associate with sodium cholate, which is hydrophilic and would be expected to be in the interior of a liposome? Applicant's response is not adequate in this regard.

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5. Claims 186-198 provide for the use of the combination, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 186-198 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Applicant indicates that the amendments overcome this rejection. These claims still recite "The use of" instead of "a method of treatment" and therefore, the rejection is maintained.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 58-98 and 100-198 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 92/03122 of record.

WO discloses a composition containing two or more amphiphilic substances with different solubilities for the administration of various active substances including insulin (note the abstract and entire publication, in particular, examples and claims).

Applicant indicates in the response that an English translation of the reference; the examiner however, is unable to find the translation in the electronic file. Therefore, the examiner is unable to address the specific issues argued by applicant. However, the examiner had already pointed out the reference appears to teach the same combination of amphiphathic substances together with the active agents such as insulin (see Examples 163-165-175 in the reference). A careful review of the examples in instant specification and those in the reference indicates the same components in similar amounts and the method of preparation appears to be the same. The rejection is maintained.

8. Claims 58-61, 63, 66-76, 91-96, 98, 101, 117, 126-127, 157-171, 174, 186, 187, 189-192 are rejected under 35 U.S.C. 102(b) as being anticipated by Uster (4,944,948).

Uster discloses a combination of three amphipathic substances and formation of vesicles. The combination includes two phospholipids, PC, PG and a macromolecule, EGF. The compositions further contain cholesterol (note the abstract, col. 4, lines 1-32 and col. 8, line 29 et seq.).

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that while the compositions of Uster might contain

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phospholipids and macromolecules, since these compositions are directed to a high viscosity formulation, they necessarily also contain zwitterionic components such as neutral amino acids all of which are not involved in surface formation of or association of a third substance in accordance with the teachings of the present invention. These arguments are not found to be persuasive since instant claim language does not exclude the neutral amino acids and others in Uster. Applicant further argues that Uster's compositions require a combination of negatively charged membrane and positively charged EGF and it is in clear contrast to the combination of present invention. Applicant also argues that according to Uster, cholesterol serves the well-defined purposes of increasing the stability of liposomes and reducing the release of EGF and thus, cholesterol is an integral part of the compositions of Uster whereas, it is only one of the number of possible membrane forming substances in the present invention. These arguments are not found to be persuasive since the differences between Uster and instant compositions as argued by applicant are not reflected in the claims. The rejection is maintained.

9. Claims 58-60, 63, 66-74, 91-98, 100-101, 110-122, 151-152, 171-180, 186, 189-192 are rejected under 35 U.S.C. 102(b) as being anticipated by Klivanov (BBA, 1991).

Klivanov discloses liposomes containing three amphipathic substances. They include phospholipids and cholesterol. The third amphipathic substance, which is on the surface, is either PEG or an antibody (note the summary and page 143). The reference meets the requirements instant claims.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that Klibanov discloses that PEG-PE or GM1 or antibody is incorporated into the membrane and even if these could fall under the class of chain or macromolecules of the present invention, Klibanov only discloses the incorporation of such substances into the membrane, which is not subject matter of the present invention. These arguments are not persuasive. The claims are given the broadest reasonable interpretation and in instant case, as applicant himself recognizes somewhat, these are macromolecules and since PEG is connected to the side chain of the phospholipid, they can be called as chain molecules. As already pointed out above, instant specification does not give precise definition of the terms. With regard to applicant's arguments that these compounds are incorporated into the membrane, the examiner points out that instant claims do not exclude this limitation. The rejection is maintained.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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6. Claims 58-98 and 100-198 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 92/03122 cited above, in further combination with either Uster (4,944,948) or Klibanov cited above.

The teachings of WO have been discussed above. In essence, WO basically teaches a combination of the three amphipathic substances claimed. What is unclear from WO is whether the third substance (macromolecule) is on the surface of the vesicles. Assuming that it is not, attaching a macromolecule on the surface, if that is desired, is deemed obvious to one of ordinary skill in the art since the reference of Uster teaches that when a macromolecule such as EGF can either be encapsulated or attached to the surface of the vesicles with the same release rates (abstract and col. 8, line 29 et seq., col. 10, line 61 et seq.). One of ordinary skill in the art would expect at least similar results. Uster further teaches on col. 4, lines 26-32 that the negative charge on the vesicles enables the EGF molecules to adsorb on the surface of the vesicles. Although Uster does not teach macro molecules other than EGF, WO teaches a variety of macro molecules and it would have been obvious to one of ordinary skill in the art based on Uster's statement that any macromolecule could be attached to the surface of the vesicles, if such is desired and with the expectation of obtaining at least similar results. One of ordinary skill in the art would be motivated to use an amphipathic molecule such as PEG since Klibanov teaches that such a use would increase the circulation time of the vesicles.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant's arguments once again pertain to the lack of teachings or

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suggestions in WO to a combination of first, second and third substances. These have been addressed above. The general arguments with regard to Uster and Klibanov have also been addressed above. Applicant argues that Uster does not describe or suggest a third amphipathic amphipathic substance. Applicant also argues that Klibanov relates to the prolongation of circulation time of liposomes and how far the substances employed for this prolongation are capable of influencing the target binding and retention of the liposomes. These arguments are not found to be persuasive since these references teach the concept of the macromolecule being at the external surface of the liposomes and the motivation to combine need not be the same as applicant's. The rejection therefore, is maintained.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of


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the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S Kishore, PhD whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308 1234.


Gollamudi S Kishore, PhD
Primary Examiner
Art Unit 1615

GSK